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MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER	
HUYNH, PHUONG N	

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1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,428	SIMMONS, LAURA	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *July 17, 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-25,28-34,36-61,63-74,96-114,116-127 and 129-133* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-25,28-34,36-61,63-74,96-114,116-127 and 129-133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-5, 7-25, 28-34, 36-61, 63-74, 96-114, 116-127 and 129-133 are pending.

2. In view of the claims amendment filed July 17, 2008, only the following rejections remain.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. Claims 25, 29, 31, 33-34, 36 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,693,762 B1 (newly cited issued Dec 2, 1997; PTO 892).

The '762 patent teaches a method of producing humanized antibody or antigen binding fragment thereof comprising the steps of (1) aligning the sequence of donor non-human immunoglobulin heavy or light chain variable region with a subgroup sequences of human heavy chain or light chain variable regions or consensus sequence or subgroups of sequences (see claim 14 step 1, claim 16 step 1 of the '762, summary of invention, col. 13, lines 8-10, col. 14, line 16-20, in particular), (2) selecting the human acceptor heavy and light chain variable regions that is most homologous (most identity) to the heavy and light chain variable regions of the donor immunoglobulin (see col. 13, lines 14-17, claim 14, step 2, claim 16, step 2 of the '762 patent,

col. 13, line 47-50, col. 16, line 5, in particular) and (3) preparing vector comprising the sequence encoding the humanized antibody and expressing recombinant DNA encoding the heavy and light chain CDRs from a donor immunoglobulin and human framework regions from the consensus sequence in host cell such prokaryotic host cells or mammalian host cells such as CHO cell (see col. 17 lines 62 through col. 18, lines 1-48, col. 40, line 20-21, claims 14 and 16, steps 3-5, claim 20, in particular). Claim 29 is included in this rejection because reference framework regions inherently encompasses all FR1, FR2, FR3 and FR4 (see claim 20 of the '762 patent, in particular). Claims 33 and 34 are included in this rejection because the term "comprising" is open ended. It expands the variable domain to include the heavy chain variable region 1, 2, and 3 from the non-human immunoglobulin heavy chain and the selected frameworks from the human consensus subgroup sequence. Thus the reference teachings anticipate the claimed invention.

Applicants' arguments filed July 17, 2008 have been fully considered but are not found persuasive.

Applicants' position is that Claim 1 has been amended and Queen does not teach any method as amended. Queen compares Ab variable regions to be modified with human Ab variable region consensus sequences. Thus, in the method of Queen, FR sequences are involved in determining which human variable region consensus sequences are selected for use in the method. See, e.g., column 13, lines 4 to 10, and lines 47 to 49, of Queen. See also claim 14, step (1) of Queen, which is directed to a method of producing a humanized immunoglobulin, comprising the step of (1) comparing the sequence of a donor immunoglobulin heavy chain variable region against a collection of sequences of human heavy chain variable regions.

The claimed methods of this invention only compare hypervariable region (HVR) sequences to other HVR sequences (i.e., human consensus sequences) in the selection of FR amino acid residues to use in the Ab humanization process. In other words, in the instant claimed methods FR sequences are not used in the comparison of sequences (e.g., mouse Ab to human consensus sequence) that selects which human FR amino acid residues are used because only HVR sequences are compared.

In response, claim 1 and dependent claims thereof are not subjected to this rejection. It is believed that Applicants meant claim 25 and dependent claims thereof.

In response to applicants' argument that the FR sequences are involved in determining which human variable region consensus sequences in the method of Queen et al, Queen et al

('762 patent) also teaches the method comprises first comparing the framework or variable region amino acids sequence of the donor immunoglobulin to corresponding sequences from the collection (consensus sequence), see col. 2, line lines 40-45, in particular). The reference variable region CDRs are also known as hypervariable region known to one of ordinary skill in the art and as evidenced by the definition at page 21, line 12-19, in particular. It is conventional to compare or align the CDRs and/or framework region (FRs) of heavy and/or light chain to the human consensus sequence for a method of preparing humanizing antibody.

Contrary to applicants' assertion that the instant claimed methods FR sequences are not used in the comparison of sequences that selects which human FR amino acid residues are used because only HVR (also known as CDRs) sequence of antibody VNERK (anti-VEGF antibody) was compared to each of the consensus sequence HVR1 regions of the heavy chain subgroups, the claimed method step (iii) of amended claim 25 inherently or implicitly compared the framework region in order to identify at least one amino acid position in any least one framework region of the selected human subgroup variable domain consensus sequence that has a different amino acid residue than of a corresponding position the a FR of the variable domain or antigen binding domain of the non-human antibody.

Note, amending claim 25 as follow may obviate this rejection.

A method of improving the yield or assembly of humanized antibody that binds to VEGF or binding fragment thereof from a host cell, comprising: (i) providing a nucleic acid encoding a humanized antibody or antigen binding fragment made by a method comprising" (a) aligning a heavy chain hypervariable region (HVR1) and/or a heavy chain hypervariable region 2 (HVR2) of a variable domain of a non-human antibody or antigen binding fragment thereof to corresponding heavy chain HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences I-III; (b) selecting a human heavy chain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the non-human HVR1 sequence and/or the non-human HVR2 sequence to provide at least one framework sequence for said humanized antibody or binding fragment thereof, (c) identify at least one amino acid position in at least one framework region (FR) of the selected human subgroup variable domain consensus sequence that has a different amino acid residue than that of a corresponding position in a FR of the variable domain of the non-human anti-VEGF antibody or binding fragment thereof, and (d) substituting at least one amino acid in the framework region (FR) at the corresponding position of the non-human variable domain of the anti-VEGF antibody or antigen

binding fragment to be the same as that of the amino acid residue identified in step (c) and (ii) expressing the humanized anti-VEGF antibody or binding fragment thereof in the host cell, wherein the humanized anti-VEGF antibody or antigen binding fragment thereof has improved yield in a host cell in culture as compared to the corresponding unmodified antibody or antigen binding fragment thereof.

6. Claims 25 and 29-31 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,558,564 (of record, issued Sept 1996; PTO 892).

The '564 patent teaches a process for the preparation of a humanized monoclonal antibody, comprising hypervariable regions (CDRs) of antigen-binding sites of non-human origin, and FRs of variable regions and constant regions of the light and heavy chains of human origin by cultivating transformed host cells in a culture medium and purifying and isolating the expressed antibody proteins (see col. 9, lines 34, in particular). The reference method comprises the steps of aligning V.sub.L and V.sub.H genes for MAb 425 are shown in FIG. 2. The amino acid sequence of the 425 V.sub.L and V.sub.H regions, are compared to other mouse variable regions in the Kabat data base (Kabat et al., 1987). The V.sub.L region can be classified into the mouse kappa chain variable region subgroup IV or VI. Within the FRs, the 425 V.sub.L region has an approximately 86% identity to the consensus sequence for mouse kappa subgroup IV and an approximately 89% identity to subgroup VI. The 425 V.sub.L region appear to use the JK4 segment. Examination of the VH region shows an approximately 98% identity to the FRs of the consensus sequence for mouse heavy chain subgroup II (B) (see col. 14, lines 1-22, in particular), select the human FRs on which to graft the mouse CDRs, the FRs of mouse MAb 425 V.sub.H region are compared with the FRs from the consensus sequences for all subgroups of human V.sub.H regions (Kabat et al., 1987). This comparison shows that the FRs of mouse MAb 425 V.sub.H are most like the FRs of human V.sub.H subgroup I showing an approximately 73% identity within the FRs and an approximately 65% identity over the entire V.sub.H regions (see col. 16, lines 29-61, in particular). The method than constructs one or several expression vectors comprising in each case at least a promoter, a replication origin and the coding DNA sequences encoding for the light and heavy chains can be present together in one or, alternatively, in two or more different vectors, and finally, transforming the host cells with one or more of the expression vectors in host cell such as COS cells (see col. 15, lines 55-65, in particular). The reference human subgroup variable domain consensus sequence comprises a heavy chain domain FR1

sequence of SEQ ID NO: 11, which is 100% identical to the claimed SEQ ID NO: 1 (see reference SEQ ID NO: 11, col. 9, lines 13, in particular). Thus the reference teachings anticipate the claimed invention.

Applicants' arguments filed July 17, 2008 have been fully considered but are not found persuasive.

Applicants' position is that as clarified by the instant amendment, Bendig does not teach any method for producing an antibody or antigen binding fragment with improved yield from a host cell, e.g., as in currently amended Claim 1, as noted above. Claims dependent from claim 1 also are distinguished from the cited art because *inter alia* of their dependency on claim 1.

Bendig, like Kolbinger and Queen, compares variable regions to be modified with human variable region consensus sequences. In fact, in one aspect Bendig takes exactly the opposite approach from that of this invention by comparing only FR sequences of mouse Ab (the Ab to be humanized) and human FR consensus sequences; see e.g., column 16, lines 26 to 36, of Bendig.

In contrast, the claimed methods of this invention only compare hypervariable region (HVR) sequences to other HVR sequences (i.e., human consensus sequences) in the selection of FR amino acid residues to use in the Ab humanization process. In other words, in the instant claimed methods FR sequences are not used in the comparison of sequences (e.g., mouse Ab to human consensus sequence) that selects which human FR amino acid residues are used because only HVR sequences are compared.

In response, claim 1 and dependent claims thereof are not subjected to this rejection. It is believed that Applicants meant claim 25 and dependent claims thereof.

Contrary to applicants' assertion that the instant claimed methods FR sequences are not used in the comparison of sequences that selects which human FR amino acid residues are used because only HVR (also known as CDRs) sequence of antibody VNERK (anti-VEGF antibody) was compared to each of the consensus sequence HVR1 regions of the heavy chain subgroups, the claimed method step (iii) of amended claim 25 inherently or implicitly compared the framework region in order to identify at least one amino acid position in any least one framework region of the selected human subgroup variable domain consensus sequence that has a different amino acid residue than of a corresponding position the a FR of the variable domain or antigen binding domain of the non-human antibody.

Further, the '864 patent (Bendig et al) also teaches the reshaped human 425 VH region is preferably designed based on the CDRs of mouse MAb 425 and FRs derived from the consensus sequence for human subgroup I FRs (see col. 16, lines 48-50, in particular).

7. Claims 25, 28, 29, 31, 33-34, 36 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,884,879 (of record, filed August 6, 1997; PTO 892) as evidenced by US Pat No 5,693,762 B1 (newly cited issued Dec 2, 1997; PTO 892).

The '879 patent teaches a method of preparing a humanized antibody or antigen binding fragment thereof wherein said antibody or antigen binding fragment thereof that binds to VEGF and has the HVR1 amino acid sequence of GYTFTYGIN (reference SEQ ID NO: 110) or GYDFTHYGMN (reference SEQ ID NO: 128) which are 100% identical to the claimed SEQ ID NO: 14 and SEQ ID NO: 18, respectively. The reference method for preparing humanized anti-VEGF antibody or antigen binding thereof by expressing said antibody having or antigen binding fragment thereof in host cell such as prokaryote *E coli* or mammalian host cell such as VERO or CHO cell (see col. 25 lines 126 through col. 26, in particular) and recovering said antibody or antigen binding fragment thereof (see col. 27, lines 35-61, in particular). The reference variable heavy chain framework (FR) sequence of the non-human monoclonal antibody has amino acids substitution from the human consensus sequence subgroup III (see col. 14, lines 34-67 through col. 15, lines 1-2, sequence alignment in Figure 1A, in particular). The reference variable light chain framework (FR) sequence of the non-human monoclonal antibody has amino acids substitution from the human consensus sequence subgroup I (see col. 15, lines 28-44, sequence alignment in Figure 1B, in particular). Although claim 25 has been amended to include the step of aligning the mouse and human HVR1 and HVR2 domains, it is known in the art as evidenced by the '762 patent that method of preparing humanized antibody begins with the step of aligning the sequence of donor non-human immunoglobulin heavy or light chain variable region with a subgroup sequences of human heavy chain or light chain variable regions or consensus sequence or subgroups of sequences (see claim 14 step 1, claim 16 step 1 of the '762, summary of invention, col. 13, lines 8-10, col. 14, line 16-20, in particular), (2) selecting the human acceptor heavy and light chain variable regions that is most homologous (most identity) to the heavy and light chain variable regions of the donor immunoglobulin (see col. 13, lines 14-17, claim 14, step 2, claim 16, step 2 of the '762 patent, col. 13, line 47-50, col. 16, line 5, in particular). As such, the method of humanized anti-VEGF antibody as taught by the '879 patent inherently has the

initial step of aligning the sequence of donor non-human immunoglobulin heavy or light chain variable region with a subgroup sequences of human heavy chain or light chain variable regions or consensus sequence or subgroups of sequences. Thus the reference teachings anticipate the claimed invention.

Applicants' arguments filed July 17, 2008 have been fully considered but are not found persuasive.

Applicants' position is that as clarified by the instant amendment, Beca does not teach any method for producing an antibody or antigen binding fragment with improved yield from a host cell, e.g., as in currently amended Claim 1, as noted above. Claims dependent from claim 1 also are distinguished from the cited art because *inter alia* of their dependency on claim 1.

Beca, like Bendig, Kolbinger and Queen, compares variable regions to be modified with human variable region consensus sequences. In fact, in one aspect Bendig takes exactly the opposite approach from that of this invention by comparing only FR sequences of mouse Ab (the Ab to be humanized) and human FR consensus sequences; see e.g., column 16, lines 26 to 36, of Bendig.

In contrast, the claimed methods of this invention only compare hypervariable region (HVR) sequences to other HVR sequences (i.e., human consensus sequences) in the selection of FR amino acid residues to use in the Ab humanization process. In other words, in the instant claimed methods FR sequences are not used in the comparison of sequences (e.g., mouse Ab to human consensus sequence) that selects which human FR amino acid residues are used because only HVR sequences are compared.

In response, claim 1 and dependent claims thereof are not subjected to this rejection. It is believed that Applicants meant claim 25 and dependent claims thereof.

Contrary to applicants' assertion that the instant claimed methods FR sequences are not used in the comparison of sequences that selects which human FR amino acid residues are used because only HVR (also known as CDRs) sequence of antibody VNERK (anti-VEGF antibody) was compared to each of the consensus sequence HVR1 regions of the heavy chain subgroups, the claimed method step (iii) of amended claim 25 inherently or implicitly compared the framework region in order to identify at least one amino acid position in any least one framework region of the selected human subgroup variable domain consensus sequence that has a different

amino acid residue than of a corresponding position the a FR of the variable domain or antigen binding domain of the non-human antibody.

Although claim 25 has been amended to include the step of aligning the HVR1 and/or HVR2 domains of non-human antibody or binding fragment with the HVR1 and/or HVR2 human consensus sequence, it is known in the art as evidenced by the '762 patent that method of preparing humanized antibody begins with the step of aligning the sequence of donor non-human immunoglobulin heavy or light chain variable region with a subgroup sequences of human heavy chain or light chain variable regions or consensus sequence or subgroups of sequences (see claim 14 step 1, claim 16 step 1 of the '762, summary of invention, col. 13, lines 8-10, col. 14, line 16-20, in particular). The '762 patent also teaches the method comprises first comparing the framework **or** variable region amino acids sequence of the donor immunoglobulin to corresponding sequences from the collection (consensus sequence), see col. 2, line lines 40-45, in particular). The reference variable region CDRs are also known as hypervariable region known to one of ordinary skill in the art and as evidenced by the definition at page 21, line 12-19, in particular.

8. The following new ground of rejection is necessitated by the amendment filed July 17, 2008.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-5, 7-25, 28-34, 36-61, 63-74, 96-114, 116-127 and 129-133 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The claims encompass innumerous modification in the framework region of heavy and/or light chain at the corresponding position of any non-human variable domain or antigen binding fragment.

The specification discloses only (1) a method for improving the yield of recombinant humanized antibody or antigen binding fragment thereof from a host cell in culture, comprising:

(i) providing a nucleic acid encoding a humanized antibody or antigen binding fragment made by a method comprising" (a) aligning a heavy chain hypervariable region (HVR1) and/or a heavy chain hypervariable region 2 (HVR2) of a variable domain of a non-human antibody or antigen binding fragment thereof to corresponding heavy chain HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences I-III; (b) selecting a human heavy chain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the non-human HVR1 sequence and/or the non-human HVR2 sequence to provide at least one framework sequence for said humanized antibody or binding fragment thereof, (c) substituting the heavy chain framework sequence of a non-human antibody or antigen binding fragment with the heavy chain framework consensus sequence with the most sequence identity identified in step (b) and (ii) expressing the humanized antibody or antigen binding fragment thereof in the host cell, wherein the assembly or yield of the humanized antibody or antigen binding fragment having framework consensus subgroup substitution is improved.

The specification also discloses (2) a method of improving the yield or assembly of humanized antibody that binds to VEGF or binding fragment thereof from a host cell, comprising: (i) providing a nucleic acid encoding a humanized antibody or antigen binding fragment made by a method comprising" (a) aligning a heavy chain hypervariable region (HVR1) and/or a heavy chain hypervariable region 2 (HVR2) of a variable domain of a non-human antibody or antigen binding fragment thereof to corresponding heavy chain HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences I-III; (b) selecting a human heavy chain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the non-human HVR1 sequence and/or the non-human HVR2 sequence to provide at least one framework sequence for said humanized antibody or binding fragment thereof, (c) identify at least one amino acid position in at least one framework region (FR) of the selected human subgroup variable domain consensus sequence that has a different amino acid residue than that of a corresponding position in a FR of the variable domain of the non-human anti-VEGF antibody or binding fragment thereof, and (d) substituting at least one amino acid in the framework region (FR) at the corresponding position of the non-human variable domain of the anti-VEGF antibody or antigen binding fragment to be the same as that of the amino acid residue identified in step (c) and (ii) expressing the humanized anti-VEGF antibody or binding fragment thereof in the host cell, wherein the humanized anti-VEGF antibody or antigen

binding fragment thereof has improved yield in a host cell in culture as compared to the corresponding unmodified antibody or antigen binding fragment thereof.

The specification discloses making changes in FR1, FR2 and FR3 region residues from human consensus subgroup III residues to the human consensus subgroup I residues of humanized anti-VEGF VNERK antibody resulted in a greater increase in antibody yield over the increase demonstrated by changing only one framework region. Substitution of all three framework region residues with the selected subgroup consensus sequence resulted in about a 3.5 fold increase in antibody yield compared to the parent antibody anti-VEGF VNERK, see page 95-96.

At the time of filing, applicants are not in possession of methods of *modifying* any one amino acid at the corresponding position of any and all non-human variable domain of the antibody or any antigen binding fragment to be the same as the different human amino acid residue identified from any subgroup consensus sequence to form any modified heavy and/or light chain FR regions in the non-human variable domain of the antibody or antigen binding fragment for the claimed methods as broadly as claimed. There is no disclosure of aligning any light chain hypervariable region (HVR1) and/or a light chain hypervariable region 2 (HVR2) of a variable domain of any non-human antibody or antigen binding fragment thereof to corresponding light chain HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences. There is no guidance as to modifying any one or more positions such as position 6, 23 or both or position 1, 11, 13, 18, 19 and mixture thereof (claims 19, 20, 21) and/or any positions of the light chain as set forth in claims 51-54, 56-57, 63, 64 to any amino acids would improve the yield of any and all non-human antibody other than the non-human antibody that binds to VEGF VNERK having the specific amino acid substitutions. Further, there is no disclosure of modifying any light chain FR region (claim 12) in the specification as filed. The specification provided little or no guidance beyond a mere statement to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the heavy and/or light chain FR as well as the coding sequence thereof which are tolerant to change (e.g. such as by amino acid substitutions, deletions, addition and/or combination thereof), and the nature and extent of changes that can be made in these positions to generalized to all antibodies. There is no guidance as to which one or more amino acids in at least one FR of heavy and light chains of all antibodies to be modified or deleted such that deletion still maintain binding specificity, and still improved the yield of antibody production (Claims 96, 100, 104, 129).

The specification does not describe the method could be generalize to other antibodies and members of the modified antibodies by structure.

Wu et al (J Mol. Biol 294: 151-162, 1999; PTO 892) teach that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity of antibody due in part to the large conformational change in antibodies that accompany antigen binding site (see Wu et al, pages 152, left col, in particular).

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Vas-Cath, Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class, where the specification provided only the bovine sequence.

Because the described method of modifying anti-VEGF to improve the yield of humanized anti-VEGF is not a representative of the entire claimed genus, one of skill in the art would conclude that applicant was not in procession of the claimed genus because a description of only a method of improving the yield of anti-VEGF antibody made by (a) aligning a heavy chain hypervariable region (HVR1) and/or a heavy chain hypervariable region 2 (HVR2) of a variable domain of a non-human antibody or antigen binding fragment thereof to corresponding

heavy chain HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences I-III; (b) selecting a human heavy chain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the non-human HVR1 sequence and/or the non-human HVR2 sequence to provide at least one framework sequence for said humanized antibody or binding fragment thereof, (c) identify at least one amino acid position in at least one framework region (FR) of the selected human subgroup variable domain consensus sequence that has a different amino acid residue than that of a corresponding position in a FR of the variable domain of the non-human anti-VEGF antibody or binding fragment thereof, and (d) substituting the residues at the specified positions 1, 6, 9, 10, 11, 12, 13, 16, 18, 19, 20, and 23 in the heavy chain FR1 subgroup III sequence for the corresponding amino acid residues in the subgroup I consensus sequence to show that the applicant would have been in possession of the claimed genus as a whole at the time of filing. Therefore, the specification fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the full scope of claims 1-5, 7-25, 28-34, 36-61, 63-74, 96-114, 116-127 and 129-133.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115). Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001 and revision of the Written Description Training materials, posed April 11, 2008 http://www.USPTO.gov/web/menu/written.pdf.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

14. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
October 24, 2008